

C<sup>3</sup>  
encl.  
33. (Amended) The *mpl* ligand of Claim 32 where X is selected from the group consisting of residue 153 to about 157.

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C<sup>4</sup>  
40. (Amended) [The *mpl* ligand of Claim 9 that contains the h]Human *mpl* ligand comprising the amino acid sequence of Figure 8 from residue 1 to residue 153.

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### REMARKS

Claims 1, 3, 4, 7, 9, 28, and 30-40 are pending and under consideration. Claims 3, 38, and 39 have been canceled. Upon acceptance of this Amendment and entry into the record, Claims 1, 4, 7, 9, 28, 30-37, and 40 will be in this case.

The specification has been amended at page 12, line 12 to correct an error made in drafting the application and to address a question raised by the Examiner in Paper No. 6, lines 24-26, regarding the number of  $\alpha$ -subunits for certain cytokine receptors. The correction adds the language "of IL5-R $\alpha$ ," which can be found in the reference cited on page 12, line 2. Since this reference is expressly incorporated by Reference (see page 102, line 35) Applicants believe no new matter has been added. The Nicola et al. Reference is enclosed for the Examiner's review. Applicants refer the Examiner to the second page of the reference where a diagram of human receptors IL5, GM-CSF and IL-3 each have an  $\alpha$ -subunit and combine with a common  $\beta$ -subunit (KH97) to form the high affinity receptor shown.

Claims 1, 9, 32-33, and 40 have been amended to overcome the Examiner's objections to the claims found on pages 7 and 8 of Paper No. 10. Applicants believe these amendments are formal and as such no new matter has been added.

### Double Patenting Rejection

Applicants acknowledge the potential for double patenting with respect to the applications set forth by the Examiner on page 3-6 of Paper No.10. This is a provisional rejection however and Applicants will cancel claims or file terminal disclaimers as necessary to avoid double patenting when a case is ready for allowance. On page 4 of Paper No. 10, ✓ the Examiner has required a showing that Application Serial No. 08/185,607 was assigned

to the same entity as the instant 08/223,263 application. A copy of the assignment in the "607 application is enclosed.

### **Objections and Rejections Under 37 U.S.C. § 112**

Applicants have canceled Claims 3, 38 and 39 rejected by the Examiner and have amended Claims 1, 9, 32, 33, and 40 as suggested by the Examiner. Applicants have included the open ended language "comprising" in Claim 40.

### **Rejections over Prior Art**

The Examiner has rejected all pending claims under either 35 U.S.C. 102 or 103 in view of two primary references by McDonald in combination with certain other references (Shadle et al.) demonstrating pegylation and Hill demonstrating combination of TPO with other cytokines. Applicants respectfully traverse this rejection.

First, as pointed out on page 11, lines 20-26 of Paper No. 10., many cytokines alone or in combination with one another have the ability to stimulate platelet production and thus have thrombopoietin-like activity. Enclosed for the Examiner's review are exemplary references showing SCF, IL-1 $\beta$ , IL-3, IL-6, IL-11, interferon- $\gamma$  and EPO all have TPO-like activity. Thus many proteins could be considered thrombopoietins based on biological activity alone. Each of these, except for McDonald, can be distinguished from the instant TPO by a different amino acid sequence. McDonald's protein can be distinguished from the instant claimed TPO by a significantly different physical property -- namely stability to heat, SDS and thiol denaturation. Note in U.S. Patent No. 5,128,449 to McDonald, column 7, line 32, the "protein" can be heated in acetonitrile to 100° C for 10 minutes! Similarly the "protein" can be subjected to mercaptoethanol and SDS-PAGE and still retain its biological activity. See McDonald et al., J. Lab. Clin. Med. 106(2) 162-174 (1985), step V in summary, step VI on page 163 and Figure 9, Page 173 which demonstrate stability to heat/SDS/mercaptoethanol. These properties of McDonald's TSH are significantly different from Applicants' TPO which is shown in Figure 1 and described on page 39, lines 4-8 of the specification, to be sensitive to heat and thiols (DTT).

Applicants submit that given these significant differences in physical properties between the prior art TSH and Applicants' TPO an adequate showing of novelty and

nonobviousness over the primary references has been made and that any rejection over the secondary references, e.g., pegylation, etc., is not applicable.

Applicants respectfully request reconsideration under 37 C.F.R. § 1.111 in view of these amendments and explanation below.

Respectfully submitted,

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